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Effect of radiation wave length upon absorption in soft tissue and in bone.

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EFFECT OF RADIATION WAVE LENGTH UPON ABSORPTION IN SOFT TISSUE AND IN BONE

NORAIR M. LULEJIAN

1951

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EFFECT OF RADIATION WAVE LENGTH UPON ABSORPTION IN SOFT TISSUE AND IN BONE

A Thesis

Presented in Partial Fulfillment of the Requirements for the Degree Master of Science

By

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1951

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I. INTRODUCTION

It is apparent to anyone who has seen an x-ray picture that bone absorbs more radiation than soft tissue. However, the tissue dose at any depth below the skin is estimated assuming that the tumor is in an infinitely large homogeneous phantom of tissue-like material. This 'phantom' is usually water or water-equivalent material. It has been recognized for a long time that the assumption of a homogeneous phantom inadequately represents the complex structure of the body, and that account should be taken of at least the larger discontinuities of structure associated with the skeleton and the air-filled lung tissues.

Spiers (1, 2) has shown that powdered hard bone of the human femur has a much greater absorption coefficient for low energy monochromatic x-rays than excised muscle or fat tissue. He determined the absorption coefficients of the various tissues using a pair of Ross balanced filters. Spiers used the wave length band between 0.42 and 0.48 Angstrom units and obtained a mass absorption coefficient for bone which was approximately four times that of muscle. Based upon this one experimental fact and some sort of assumption of the electronic content of bone, Spiers made extensive calculations concerning the energy absorption in air, muscle tissue, fat tissue, and bone. From this he

deduced that at low x-ray energies (100 kilovolts or less) bone received three to four times the dose received by normal soft tissue. As mentioned above, the relatively white outline of the bones in an x-ray picture confirms Spier's suspicions. But whether energy absorption is the final parameter of radiation dosage remains for future clarification.

In comparison with many other tissues, the experimental investigation of the radiosensitivity of bone has been limited. This is due primarily to the fact that there is no obvious "reaction" as in soft tissue nor erythemal dose which can be observed clinically by relatively simple methods. Hence a search of the literature is indicated in order to detrmine and evaluate the experimental and clinical evidence of the radiosensitivity of bone.

II HISTORICAL REVIEW

1. Arthur Desjardins (3) gives a very complete review of the literature up to 1930. He reports that Perthes in 1903, and Recamier and Tribondeau in 1905 demonstrated that bone growth in young animals was definitely retarded by roentgen rays, but that no perceptible histological changes could be found in the hard bone due to radiation. In 1906 Forsterling exposed half the body of rabbits to irradiation. The animals exhibited marked retardation of

growth . In 1910 Cluzet fractured the leg bones of test animals, and then exposed the animals to local irradiation at the site of the fracture. Callus formation was delayed in the exposed animals. Then Cluzet first exposed the legs to irradiation and then caused the fracture, callus formation was again delayed. This was taken to indicate that the rays act on the bone cells and not directly on the callus. In 1909 Krukenberg carried out irradiation on dogs and produced the typical retardation of growth even when the dose was less than that required to cause the skin to react. In 1929 Wynen bored holes in thick bone and inserted the roots of horse beans into the holes, similar roots were inserted through muscle and both the bone and the muscle were exposed to the same dose of roentgen rays. At first the seedlings grew at the same rate, but after the eighth day there was a marked retardation in the growth of the seedlings placed within bone as compared to those placed within muscle. Wynen concluded that the seedlings in bone received a greater amount of scattered radiation than those placed in muscle.

2. Colwell and Russ (4) state that adult bone is relatively radioresistent to x-ray and that injuries from this cause are rare, since they have not observed any injury to bone or cartilage out of hundreds of cases of irradiation of mammary cancer. However, they

go on to state that the unprotected hands of the pioneers did develop undue fragility and decreased bone density. This was attributed to vascular changes which impaired bone nutrition. Hence we conclude that Colwell and Russ are of the opinion that adult bone is radioresistent, but that radiation may cut off the blood supply to the bone thus causing an indirect type of damage which may become evident after years of chronic exposure as in the hands of the pioneers.

3. Watson and Scarborough (5) discuss the subject of osteoradionecrosis very thoroughly. They attribute the development of osteoradionecrosis to irradiation, trauma and eventually to infection. They report that Regaud considered lamellar bone radiosensitive, but that Nageotte considered bone cells more radiosensitive than the lamellae. Ewing agrees with the latter point of view. He believes that the bone cells are killed first and then the changes in the lamellae follow. According to Watson and Scarborough the following histological changes are produced in bone by irradiation:

a. Periosteum is highly susceptible to irradiation. After sizeable therapeutic doses gross swelling and thickening occur and the periosteum strips easily from the bone. Histologically the inner surface of the periosteum presents a thick hyaline layer without

cells. The layer of osteoblasts usually found on the inner surface of the periosteum in contact with the bone may be absent. This explains the lack of bone regeneration. The arterioles may be strangulated by post irradiation swelling of all the coats comprising the walls of these vessels.

b. Bone exhibits osteoporosis following irradiation. The trabeculae are narrowed and irregular and the volume of the fatty marrow is increased. Extensive obliterative sclerosis of the nutrient vessels takes place. Bone cells stain poorly with hemotoxylin and eosin. The lamellar bone appears hyaline and very brittle. Canaliculi are closed and the capillary circulation is imperfect.

According to Watson and Scarborough the bone has a definite and peculiar gross histological architecture somewhat as follows:

> Bone cells are derived from osteoblasts which have been inclosed in a bone space or lacuna. These bone cells are connected one with the other and receive nourishment through very fine processes known as canaliculi. The outer surface of bone receives a large portion of its nourishment from the periosteal blood vessels which enter the outer bone through Volkmann's canals.

The blood vessels of the haversian canals and the nutrient artery supply the deeper portions of the bone and marrow. This blood system forms a rich vascular network enclosed in a rigid framework of bone tissue, the structure of which makes it highly vulnerable to the effects of irradiation.

4. Ewing (6) believes that the calcium content of bone makes it more absorbent to radiation and that scatter from bone is increased in the form of secondaries which 'burn' the periosteum .

5. Dalby et al (7) were the first in America to report damage to the bone due to irradiation. They site fourteen cases of the fracture of the femoral neck following irradiation. It is their contention that this is a significant finding since it represents an incidence of 2.1% and they maintain that the normal incidence for this age group without irradiation should be 0.03%. They also report that the average time interval from onset of pelvic malignancy to fracture was approximately three years, the patients were from 42 to 78 years old, and that none of the patients showed any sign of callus formation ten months after the fracture was observed. The radiation employed was 200 kilovolt x-rays with 0.5 mm. of Copper filter. The dose was 200 r to each of four areas every second to fourth day until a total of 1500 to 2000 r was reached within a per-

iod of approximately one month. Two or three such series of treatments were given at intervals of three to six months. The total dose ranged from 7,000 r to 22,000 r. Some of the patients were also given radium treatment, but Dalby and his collaborators believe that radium as generally employed (in 1936) probably had little effect on the fracture of the femoral neck. They base this hypothesis upon the fact that three of their patients developed femoral fractures without any radium treatment receiving only 200 kilovolt x-rays. Dalby reports that the area of fracture showed pseudoarthrosis, rarefaction of the bone substance replaced by plentiful connective tissue deficient in blood vessels. Head of femur showed absorption of bone and widening of marrow spaces.

6. Stewart (8) makes the statement that osteoradionecrosis is more prevalent (remember this is 1938) since the advent of 'high voltage' roentgen ray therapy for the treatment of cancer. He also states that Dentists, who do not use roentgen rays (still 1938), nevertheless are the first to recognize and report osteoradionecrosis. He also makes the statement that necrosis of the jaw is brought about by radium, roentgen rays, arsenic, phosphorous and thorium, but he gives no substantiating evidence for these statements. Stewart claims that of the bones of the head the mandible

is the most radiosensitive (since it has the poorest circulation) next in the order of sensitivity is the maxilla and finally the bones of the skull are considered the most radioresistent. However, it should be noted that Camp(9) has reported five cases of necrosis of the calvarium from irradiation, and in this connection Camp states that since the calvarium does not function as a weight bearing structure the symptoms of necrosis are liable to be overlooked. Here is what Stewart has to say concerning the changes that occur in bone following irradiation and concerning the structure and physiology of the bone:

> Bone receives its greater portion of nourishment from the periosteum and from nutrient arteries situated around the ends of long bones supplied by the capsular arteries. The marrow also aids in bone nutrition. Vascular anastomosis in bone is circumscribed by the following two conditions: absence of large intercommunicating vascular channels; and relative constriction of the channels by non-expansive bone structure. The branches of the haversian system are enclosed by bone lamellae in which are found lacunae containing bone cells. The lacunae intercommunicate through fine canaliculi. Bone has a relatively

high calcium content which has a high atomic weight. According to Ewing calcium produces an unusual amount of secondary radiation and is less penetrating and is more caustic. Radiation osteitis is produced by a combination of radiation and infection. Dead bone favors growth of bacteria throughout the haversian system including the canaliculi. Strong irradiation of bone will cause productive osteitis which is usually followed by noticeable thickening of the shaft of the bone at the expense of the marrow cavity. The use of intense radiation in or about the bone, especially when infection is liable to follow, should be avoided. Destruction of carcinoma by radiation at the gingiva nearly always causes loss of the corresponding segment of bone. Those body tissues and cells which have a less extensive vascular supply and anastomosis have a lower therapeutic and pathologic safety factor. Tissues degenerate physiologically and structurally when the blood supply is insufficient because of the impairment of venous return. Present knowledge (as of 1938) of the anemias and of generalized infection of bone demonstrates that bone must not be classified as an inert substance. Bone is probably one of the most highly specialized tissues in the body.

7. Camp (9) reports on five cases of radiation necrosis of the calvarium. He believes that this is due primarily to strangulation of the blood vascular system in the area by radiation. He believes that radiation is able to produce profound changes in the lamellar structure of the bone and renders it very brittle. The delicate cellular processes in the canaliculi are especially susceptible to radiation according to Camp. The long delay in sequestration and resistance of the tissue to solution are probably the result of injury and sclerosis of blood and lymph vessels in the haversian system, periosteum and surrounding tissues. Camp states that in view of the delicate nature of the cytoplasmic processes connecting bone cells through the fine canalicular system, on which the activity of the bone matrix is dependent for nutrition, the danger of injury to the bone by direct and secondary rays is apparent. His patients who showed necrosis of the calvarium received doses which ranged from 500 r to 15,000 r given over a period of months at the rate of 500 r in forty five minutes using 200 kilovolt x-rays with little filtration (0.5mm Al). Necrosis was discovered five, ten or fifteen years after irradiation.

8. Strauss and McGoldrick (10) state that if enough radiation is administered to bone, the vascular, perios-

4. Gray (4) reports on five cases of partial removals of the calvarium. He believes that little has primarily an interruption of the blood vessels [illegible] due to the late vascular lesions. He concludes that irradiation is able to produce profound changes in the [illegible] structure of the bone and marrow in very subtle. The delicate cellular processes in the [illegible] are decidedly susceptible to radiation according to Gray. The long delay in degeneration and involvement of the tissue to radiation was probably due, perhaps, to injury and sclerosis of blood and lymph vessels by the irradiation system, [illegible] and necessarily [illegible]. Gray states that in view of the delicate nature of the cylindrical processes connecting bone cells through the fine canalicular system, which the activity of the bone depends is probably [illegible], the degree of injury to the bone by direct and secondary ways is apparent. The patients who showed necrosis of the calvarium received doses which ranged from 500 r to 11,000 r given over a period of months at the rate of 150 r in twenty five minutes using 200 kilovolt x-rays with little filtration (0.5mm Al). Necrosis was diagnosed five, ten or fifteen years after irradiation.

5. Stevens and [illegible] (22) state that if enough radiation is administered to bone, the vascularity under-

teal and osseous changes will result in serious complications. They showed instances of the fracture of the femoral neck after roentgen therapy. The involved bone had not been invaded by secondary infection, therefore Strauss and McGoldrick assumed that the fracture was caused by irradiation. They also report a personal communication from Pack who mentions five cases of rib fracture following radiation therapy for mammary cancer (which discounts somewhat the above-mentioned statements of Colwell and Russ). They say that roentgenograms are of little value in earlystages of the disease, indicating that osteoradionecrosis occurs years after irradiation.

9. According to Bloom (11) many investigators have reported the effects of x-rays on growth of the long bones, but few have attempted to correlate these effects with histological changes. He also makes the following statement: " .... the stuntung of bone growth has frequently been described as an effect of x-ray treatment and demonstrated by roentgenograms, although histological observations were often incomplete and contradictory. " Bloom reports that maximum damage to the bone occurs at the growing end. In rats exposed to 600 r of total body x-radiation (which is LD_{50}/30 days) Bloom found some dead osteocytes in the lamellae of the spongiosa but not in the dense cortical bone. He also found

that osteoblasts disappeared after irradiation but gradually reappeared after some weeks. He describes the effect of 800 r of total body irradiation on the marrow of the rabbit as follows: " The major effects of exposure to 800 r of x-rays (200KV unfiltered), the $LD_{50}/30$ days for rabbits, were the destruction of most of the hematopoietic cells and their replacement by a gelatinous type marrow, which later was transformed into a fatty marrow in which hematopoietic cells began to regenerate." Bloom believes that since the depleted marrow was first replaced by gelatinous material and then fat cells, then these fat cells must be associated with the beginning of repair effects.

III THEORETICAL CONSIDERATIONS

A. Absorption of Gamma Rays

In order to determine the absorption of energy in the different tissues such as bone, muscle, etc., it is necessary to have an accurate knowledge of absorption coefficients as a function of gamma ray energy and atomic number of the absorber. The expression for absorption of radiation, $dI/dx = -mI$, tacitly assumes that radiation removed from the beam is absorbed. In reality, however, the 'absorbing' material may scatter radiation as well as absorb it in a manner somewhat similar to the effect of ground glass on visible light. Hence by absorption we are referring to the reduction in intensity of the incident beam as it passes through matter. The mass absorption coefficient, m/d, represents the sum of all the processes by which radiation is reduced in intensity in passing through an absorber, where

$$m/d = p/d + s/d + q/d \qquad \text{.............. Eqn 1}$$

m = total absorption coefficient
p = photoelectric absorption coefficient
s = Compton scatter-absorption coefficient
q = pair production coefficient
d = density in grams/cubic centimeter.

A study of the literature reveals surprisingly large discrepancies in the absorption coefficients as quoted by various authors. Theoretical formulations of

the absorption coefficients may be inerror by ten percent or greater for the higher atomic number elements. The main reason for this discrepancy is due to the various approximations which enter the theoretical calculations of cross-sections for photoelectric absorption and for pair production.

1. Photoelectric Effect

Gamma rays of low energy are absorbed mainly by the photoelectric ejection of orbital electrons from atoms of the absorbing medium. This is a resonance phenomena in which the energy of a photon is transferred to a single electron, ejecting it from the atom. At very low energies the most probable direction taken by the ejected photoelectron is normal to the incident gamma ray (because it is ejected parallel to the electric vector of the electro-magnetic radiation). As the energy of the gamma ray is increased, the electron is accelerated by the electric field as before, but it is now also deflected in the forward direction by the magnetic field component of the incident photon, where the forward direction is taken as the direction of the incident photon.

Heitler (12) states that the photoelectric cross section of the K shell is proportional to Z^5 , where Z is the atomic number of the absorbing element. In arriving at this conclusion Heitler assum-

ed that the Born approximation is valid (that is, Z/137 is very much less than unity). Hulme (13) made exact calculations for the heavier elements using energies up to 2 Mev and he concluded that the theory based upon the Born approximation which lead to the Z^5 postulate is at best only an order of magnitude estimate of the photoelectric cross section. Snyder (14) suggests that the Z^5 'law' may actually approximate the photoelectric cross section for low atomic number elements if the Sauter formula is used and multiplied by the Strobbe correction factor(both referenced in Snyder's publication). The effect of the electron shells other than the K shell may be calculated from the empirical relation that the K shell is responsible for about 80% of the total absorption. Hull and Kurita (15) have obtained some theoretical justification for this rule. The abovementioned considerations indicate that it is difficult to evaluate the accuracy of theoretical calculations of the photoelectric absorption coefficient. In general the existing theoretical calculations are confirmed by experiment within narrow limits , but errors of 5% for light elements and 10% for the heavier elements may be expected. Cuykendall (16) and Jones (17) have shown from experimental considerations that the photoelectric absorption coefficient is well described for a limited range of Z, and in

the limits of the x-ray wave lengths by the empirical formula

$$p' = k\,Z^{u}\,a^{v} \qquad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \text{Eqn 2}$$

where, $p' = p/\text{atom}$

a = wave length of incident radiation

$u = f(Z, a)$

$v = g(Z, a)$.

Cuykendall measured the mass absorption coefficients for C, Na, Al, S, K, Ni and Cu using a 600 kilovolt x-ray source and selected wave lengths of from 0.05 to 0.209 A. Cuykendall indicates that 'u' is a slowly varying function of the energy where 'u' decreases slowly from a value of 3.9 for 0.09 Mev to 3.56 for 0.20 Mev x-rays for the relatively light weight elements that Cuykendall used. Whereas according to Jones, who used higher atomic number elements (Z greater than 40), 'u' increases slowly from a value of 3.55 for 0.09 Mev x-rays to 3.88 for 0.20 Mev radiation. Hence we are justified in our above-indicated notation that 'u' is a function of atomic number and wave length. Cuykendall also showed that 'v' has a value of 2.6 for Aluminum and changes to a value of 2.83 for Copper. Jones indicates that 'v' has a value of 2.79 for Z = 41 and slowly decreases (but not linearly) to a value of 2.60 for Z = 82. Hence we are justified in writing, as above, that 'v' is some sort of a function of atomic

number and wave length (that is, $v = g(Z,a)$). Spiers (1) uses a formula attributed to Walter (1929) where the photoelectric absorption coefficient of an element may be written as follows:

$$p = (d/A)(N k Z^{3.94} a^3) \qquad \text{.........Eqn 3}$$

where

A = atomic weight of absorber

N = Avogadro's Number = 6.023×10^{23}

d = density

k = 2.64×10^{-26} when a is given in Angstroms.

It should be remembered that Spiers, in using the relation of Walter, has tacitly assumed that 'u' and 'v' of the Cuykendall relation (see Eqn 2) are constants. Other empirical formulae of the mass absorption coefficient are as follows:

$$p/d = (NZ/A)(1.04\times10^{-30} Z^3 E_g^{-4}(1 + 0.0083 (E_g - 0.25 E_k - 0.488 E_k^2))$$

where $\qquad$ .... Eqn 4

E_g = energy in Mev

E_k = K absorption limit in Mev.

Eqn 4 was advanced by Grey (18) in 1927

Lea (19) proposed the following equations in 1947:

$$p/d = (N/A)(1.48\times10^{-26} Z^{4.1} a^n) \qquad \text{....... Eqn 5}$$

where n = 3.05 for elements C, N and O

n = 2.85 for elements from Na to Fe.

However, Lea also states that the photoelectric absorption coefficient for the different compounds have different formulations such as:

(p/d) of air $= 2.05\ a^{3.05} + 0.41\ a^{2.85}$

(p/d) of water $= 2.50\ a^{3.05}$ ... Eqns 6

(p/d) of wet tissue $= 2.26\ a^{3.05} + 0.27\ a^{2.95}$

(p/d) of virus protein $= 1.56\ a^{3.05} + 0.07\ a^{2.85}$

Victoreen (20) proposes the following formulation:

$p/d = C_k\ a^3 + D_k\ a^4$ .... Eqn 7

where

$C = (1/a_1a_2)(3\ \ e^2/mc^2\ )(N/A)$

$D = (1/a_1a_2a_3)(3\ \ e^2/mc^2\ )(N/A)$

where a_1, a_2 and a_3 are the critical wave lengths such that $1/a_e = R(Z-t)^2(1/n_1^2 - 1/n_2^2\ ) +$

$R(\ \&^2(Z-t)^4(1/n_1^4 - 1/n_2^4\ )(1-3/4) + ..)$

where R = Rydberg constant

t = screening constant

n_1 and n_2 are integral quantum numbers

$\&$ = Bohr-Sommerfeld fine structure correction for hydrogen-like atoms.

From a study of the above mentioned formulae for the photoelectric absorption coefficient we see that the latter is really a function of Z and a, and that no exact formulation exists for this cross section. Fortunately at higher energies and at low or moderately low values of Z with which we are concerned, the photo-

electric absorption coefficient is relatively less important than the Compton scatter-absorption coefficient.

2. Compton Effect

In the Compton effect the photon is not absorbed but instead undergoes a reduction in energy and a deflection from its original direction. Thus a collimated beam of monoergic gamma rays after traversing an absorber is partially degraded in energy and spread over a wide angle by scattering. Compton first described this in 1923 by considering the interaction between the photon and the electron as a classical two body collision, and derived the following relation between the scattering angle and the change in wave length:

$$a' - a = (h/m_0c)(1 - \cos \&) = 0.0242(1 - \cos \&) \qquad \text{....... Eqn 8}$$

where

$\&$ = angle of scatter

a' and a are the initial and scattered wave lengths. The factor $h/m_0c = 0.0242$ angstrom, known as the Compton wavelength, is the shift in wavelength for any gamma ray scattered through an angle of ninety degrees. The scattering angle may take any value from zero to pi. According to Siri (21) " ... it is apparent that on the average after one or two collisions, high-energy gamma rays are degraded to wavelengths in the order of a Compton wavelength. Further scattering then has

lessmarked effect, and the photon is more likely to be absorbed subsequently by the photoelectric effect."

A quantum mechanical treatment of scattering that is valid for all gamma ray energies has been carried out by Klein and Nishina on the basis of Dirac's relativistic theory of the electron, and the formulae are given below (as indicated in Siri's text):

$s/d = (NZ/A)\, s_e$ .... Eqn 9

where

s_e = total Compton scatter-absorption coefficient per electron.

$s_e = {}_s s_e + {}_a s_e$ .... Eqn 9a

where

${}_s s_e$ = is the scattering cross section arising from the loss of photons scatterd out of the incident beam of radiation.

${}_a s_e$ = is the absorption cross section which accounts for the reduction in intensity of the incident beam due to loss in energy suffered by the scattered photons which make inelastic collisions with the electrons of the absorber.

$$s_e = y\big(2(1 + \&)^2/ \&^2(1 + 2\&) - (1 + \&)/ \&^3 \ln(1 + 2\&) - (1 + 3\&)/(1 + 2\&)^2 + (1/2\&)\ln(1 + 2\&) \big)$$

where .... Eqn 9b

$y = 2\pi e^4/m_0^2c^4$

$\& = hv/m_oc^2 = E_\gamma/0.51$ where E is in Mev

$$
\begin{aligned}
{}_a s_e = y\big(& 2(1+\alpha)^2/\alpha^2(1+2\alpha)^2 - (1+3\alpha)/(1+2\alpha)^2 \\
& + (1+\alpha)(1+2\alpha-2\alpha^2)/\alpha^2(1+2\alpha)^2 \\
& - 4\alpha^2/3(1+2\alpha)^3 - \\
& -\big((1+\alpha)/\alpha^3 - 1/2\alpha + 1/2\alpha^2\big)\ln(1+2\alpha)\big).
\end{aligned}
$$

.... Eqn 10

From a study of the above equations it is evident that s_e is independent of Z, so that once it is calculated for a desired energy range the curve may be applied to any absorbing material by multiplying it with the appropriate constants. It is also apparent that s_e is directly proportional to the electronic density of the absorbing medium.

Since the objectives of this thesis depend to a large extent upon the validity of the Compton scatter-absorption coefficient, a search has been made of the literature to determine the accuracy of the Klein Nishina equations by noting to what extent the calculated values agree with the experimental results. Hewlett (22) as well as Allen (23) have measured the absorption of low energy radiation (0.12 Mev to 0.04 Mev) in Carbon, and their experimental findings agree well with the Klein Nishina equations. Lauritsen (24) confirmed the equations for gamma ray energies of from 0.24 Mev to 0.60 Mev using Carbon and Aluminum as the absorbers. Parkin-

son (25) determined the scattering cross section in Al using gamma ray energies of 1.11, 1.71 and 2.76 Mev by two independent methods and found his measurements in agreement within experimental error with the Klein Nishina equations. Other references which have also confirmed the formulation are: (26), (27) and (28). G.D. Adams (29) tested the Compton absorption-scatter coefficient at high energies (11 Mev to 22 Mev) using x-rays from a 22 Mev betatron. He found that the experimental values of the total absorption coefficient in lead were too low as compared to the theoretical computations. However, Adams concludes this discrepancy is due wholly to the errors inherent in the computations of the pair production coefficient, and that the Compton scatter-absorption coefficient as calculated from the Klein Nishina relation agrees well with the experimental results. Hence we have indicated by this survey of the literature that there exists definite proof of the validity of the Klein Nishina formulae for an energy range of from 0.50 Mev to 20 Mev. This type of accuracy is not possible for the photoelectric or pair production coefficients which remain at best empirical in nature.

3. Pair Production Effect

When a gamma ray is completely absorbed it may give rise to an electron-positron pair provided the incident photon has an initial energy of 1.02 Mev or grea-

ter. Bethe and Heitler (30) give the following formula for the pair production coefficient using the Born approximation:

$$q = (28/9)a\, r_0^2\, Z^2(\ln 2g - 109/42) \qquad \ldots\ldots \text{ Eqn 11}$$

where

$g = E/m_0c^2$

$a = e^2/hc$

$r_0 = e^2/m_0c^2$.

Since the Born approximation is not valid for the higher atomic number elements, the theoretical calculations of q are not expected to conform to the experimental values especially for the higher Z values. Adams (29) who measured absorption coefficients of the elements using high energy quanta, states that the calculated value of the pair production coefficient is too high in the case of lead and too low for copper but is valid for aluminum and iron. This really indicates the empirical nature of the pair production coefficient. In addition to the principle effect of pair production in the nuclear Coulomb field, there is a small contribution due to pair production in the fields of atomic electrons which is approximately proportional to Z. Watson (31) and also Adams(29) state that if the Z^2 term of the above-mentioned Heitler formula (Eqn 11) is replaced by $Z(Z + 1)$ then the 'triplet' formation is taken into account.

An approximate formula for the computation of the pair production coefficient per electron for radiation energies up to 5 Mev has been given by Hirschfelder ([illegible]) which is as follow:

$$q/\text{electron} = 2.87\text{x}10^{-28}\, Z(E_g - 1.19) \quad \text{..... Eqn 12}$$

where

E_g = energy of incident photons in Mev.

Therefore

$$q/d = (NZ/A)(q/\text{electron}) = (NZ/A)\, q_e \quad \text{.......Eqn 12 a}$$

which shows that according to Hirschfelder's approximation q/d is proportional to Z^2, but note that this approximation is not valid above 5 Mev. For higher gamma ray energies (where E is much greater than 0.5 Mev but less than 137 $m_0c^2\, Z^{-1/3}$) Heitler and Sauter (33) have given the following equation:

$$q_e = (e^2/m_0c^2)^2(Z/137)(\ (28/9)(\ln(2hv/Z) - 2/27)\ ) \quad \text{........... Eqn 13.}$$

We note from the foregoing considerations that since the electronic Compton absorption-scatter cross section, s_e, is independent of Z, then Compton scatter is relatively more important in low atomic number elements, and photoelectric absorption and pair production are more important in the high atomic number elements. Responsible for this is the fact that p_e is proportional approximately to Z^3 and q_e is somewhat proportional to the first power of Z.

B. Criticism of the Use of 'Effective Atomic Numbers' for Compounds

Spiers (1, 2), Hayward (33) and Wilson (34) have used the concept of assigning an effective atomic number, $\overline{Z}$, to compounds. The effective atomic number concept was first used for low energy photons so that the pair production coefficient could be neglected. Spiers then assumed that 'u' and 'v' of Eqn 2 are constants, since he used Eqn 3 originally used by Walter. If we accept Eqn 3 then we can write the mass absorption coefficient as follows:

$$m/d = (NZ/A)(s_e + k Z^{2.94} a^3) \quad .... \text{Eqn } 14.$$

On the basis of Eqn 14 it would be possible to write the mass absorption coefficient of a compound as follows:

$$(m/d)\ \text{Compound} = w_1 m_1/d_1 + w_2 m_2/d_2 + \text{-----} . \quad \text{Eqn } 15$$

where

w_n = weight percent of element n in the compound.

Eqn 15 can also be written as

$$(m/d)\ \text{Compound} = (w_1 N Z_1)/ A_1(s_e + k Z_1^{2.94} a^3) + w_2 N Z_2/A_2(s_e + k Z_2^{2.94} a^3) + \text{--}. \quad \text{Eqn } 16$$

Spiers has rewritten Eqn 16 x as follows:

$$(m/d)\ \text{Compound} = N(w_1 Z_1/A_1 + w_2 Z_2/A_2 + \text{--})(s_e + ka^3(a_1 Z_1^{2.94} + a_2 Z_2^{2.94} + \text{--})) \quad \text{Eqn } 17$$

where

$\&_1$ = fractional electron content of element Z_1.

$= w_1 Z_1 / A_1(w_1Z_1/A_1 + w_2Z_2/A_2 + ---)$.

From the above mentioned considerations Spiers defines the effective atomic number of a compound, $\overline{Z}$, as follows:

$$\overline{Z} = (\&_1 Z_1^{2.94} + \&_2 Z_2^{2.94} + ---)^{1/2.94} \quad \text{...Eqn 18.}$$

The above definition of effective atomic number may be valid for a very limited range of energies and only if the pair production coefficient can be neglected. In reality we have no justification in assuming, as Spiers did, that 'u' and 'v' of Eqn 2 are constants. Also when the pair production coefficient is taken into account then we are forced to define not one but actually two separate effective atomic numbers for one compound. And even if we accept the unusual concept of attaching two effective atomic number to one absorber the conditions are still not satisfied for no exact formulation exists for the photoelectric or the pair production coefficients. For example, if we wish to take into account the pair production coefficient we must make the assumption that $q_e \sim Z$ which is valid only up to energies of 3 Mev as indicated by Hirschfelder (32), then this new $\overline{Z}'$ is:

$$\overline{Z}' = \&_1 Z_1 + \&_2 Z_2 + \text{-------} . \quad \text{...... Eqn 19.}$$

Some examples may make the confusion arising out the use of $\overline{Z}$ evident: $\overline{Z}$ for water is 7.42, but its $\overline{Z}'$ is 6.60, but the average atomic number of water is 7.22; $\overline{Z}$ for bone is 13.8, but its $\overline{Z}'$ is 10, and the average atomic number

is 9.3. It is my suggestion that no attempt be made to assign any effective atomic number to a compound , instead , we should content ourselves with expressing the mass absorption coefficient of a compound as follows:

$$(m/d)\ \text{Compound} = n_o(\, s_e + p_e + q_e \,) \qquad \text{... Eqn 20}$$

where

$n_o = {}_{i}\ N_i\, Z_i\, w_i \,/\, A_i = \#$ of electrons/gram of comp.

It is interesting to note that n_o is a maximum for hydrogen, therefore any compound which has a high weight percent of hydrogen will have a large Compton scatter-absorption coefficient. All other elements have approximately the same n_o since they all have their Z/A ratio equal to approximately one half, but the Z/A ratio of hydrogen is unity. Hence the mass Compton scatter-absorption coefficient of hydrogen is greater than that of Uranium. In view of this it is just as important to determine the weight percent of hydrogen in a compound as it is to determine the high atomic number elements in a compound. This is because the photon undergoes multiple scatter when it passes through thick absorbers and the original photon energy is degraded to such a point that the photoelectric effect becomes more probable. It is also our contention that the general practice of assuming that the Compton scatter coefficient, ${}_s s$, (see Eqn 9a) is not involved in the absorption process is not valid. It is my assumption that the concept of effective atomic num-

ber leads to confusion and should be avoided in biological work. Since the approximate chemical composition of most of the tissues is fairly well known we should focus our attention upon the electronic content of the compound and upon the relative weight percent of the constituent elements rather than making effective atomic number calculations of the compound.

C. Calculation of Absorption Coefficients of Some Tissues.

A comparison was made of the absorption coefficients obtained by the various investigators. It was decided that the theoretical calculations of Victoreen (20) most closely approximated the experimental results of Cuykendall (16) and Jones(17) for low energy gamma rays. For energies above one Mev the comprehensive work of Snyder (14) was considered satisfactory for our purposes. The absorption coefficient curves at the one Mev point were matched pictorially. Figure 1 shows the mass absorption coefficients of the following elements: H, C, N, O, Na, Mg, Al, P, A and Ca. From these values we have calculated the mass absorption coefficients of air, water, soft tissue and bone. The results agree well with the available experimental values. The following compositions for the different tissues were assumed in calculating mass absorption coefficients:

Table I

Element	Z	A	Weight percent of compound					
			Air	water	soft tissue	young bone	average bone	old bone
H	1	1.008		11.2	10.0	8.5	5.3	5.5
C	6	12.01			12.0	10.2	3.6	6.6
N	7	14.01	75.5		4.0	3.4	1.0	2.2
O	8	16.00	23.2	88.8	73.0	62.05	61.42	40.15
Na	11	23.00			0.10	0.16	0.02	0.16
Mg	12	24.32			0.04	0.10	0.31	0.10
P	15	30.98			0.20	4.5	8.88	14.0
S	16	32.07			0.20	0.14	0.05	0.14
Cl	17	35.46			0.10	0.16	0.025	0.16
A	18	39.94	1.3					
K	19	39.10			0.37	0.06	0.093	0.06
Ca	20	40.08			0.01	15.38	19.302	30.38

In the calculation of average bone it has been assumed that 25% of bone is water, 25% is organic matter equivalent to soft tissue and 50% is ash; and that the ash contains 88% $Ca_3(PO_4)_2$; 10% $CaCO_3$ and 2% $Mg_3(PO_4)_2$. This average bone was selected to conform to the bone reported by Spiers (1) and Wilson (34). As indicated previously, the mass absorption coefficients of the above mentioned compounds have been calculated using the following type of general formula:

$$m/d = N(\;{}_{i} (Z_i w_i/A_i) s_e + k a^V \;{}_{i} Z_i^u w_i/A_i$$

$$+ c(E_g - 1.19) \;{}_{i} Z_i^2 w_i/A_i$$

.... Eqn 21.

The results of these calculations are drawn in figure 2, and in this figure we have also drawn the $(m/d - {}_s s/d)$ term for air and for average bone. Most workers choose to call the $(m/d - {}_s s/d)$ term the 'real' mass absorption coefficient.

However, it is our opinion that in the clinical application of radiation to the human body the real absorbption of energy depends more nearly upon the m/d term than upon the $(m/d - {}_{s}s/d)$ term. It is true that the Klein Nishina relation states that the ${}_{s}s$ term represents the scattering cross section arising from the loss of photons scattered out of the beam, but this applies to an ideally thin beam of photons passing through a very thin absorber such that the intensity of radiation before and after passage through the absorber is not essentially changed. Certainly it would be a gross exaggeration to assume that this applies to the actual conditions encountered clinically. In Table II we have listed the two ratios, r_1 and r_2 where:

$r_1 = (m/d)$ ave bone / (m/d) air

$r_2 = (m/d - {}_{s}s/d)$ ave bone / $(m/d - {}_{s}s/d)$ air.

Table II

Energy in Mev	r_1	r_2
0.01	4.90	5.07
0.02	4.38	5.32
0.03	3.31	5.52
0.04	2.32	5.00
0.05	1.88	4.40
0.06	1.62	3.90
0.07	1.44	3.14
0.08	1.32	2.70
0.10	1.22	1.93
0.20	1.11	1.21
0.30	1.05	1.07
1.00	1.0	1.0

In Figure 2a we have drawn the absorption coefficients of average bone as calculated by the theoretical methods previously indicated, and we have compared these with the values given by Spiers (1). It should be noted that although Spiers assumed that the electronic content of bone was 3.0 $x10^{23}$/gm, we have shown that the value of 3.3$x10^{23}$/gm is probably more likely true merely from the knowledge of the chemical composition of bone. It is our recommendation that the electronic content of absorbing materials be determined theoretically as indicated previously in this thesis, for the results seem to justify this procedure.

D. Determination of the Energy Spectrum of Different Energy X-Ray Beams.

We have determined the energy spectrum of 100 kilovolt unfiltered x-rays, 200 kv filtered and 400 kv filtered x-ray beams. The details of the different beams are listed below:

The 100 kv x-ray beam without filter has a half value (HVL) layer of 2.6 mm Al which indicates that the average energy in the beam is 22 kv and the average wave length is 0.546 A. Since the maximum energy of the beam is 100 kv, the minimum wave length is 0.45 A. We have taken into consideration all of the beam from a wave length of 0.45 A to 1.2 A.

The 200 kv x-ray beam with 1 mm Cu filter has an HVL of 1.5 mm Cu, hence an average beam energy of 95 kilovolts

and the average wave length is 0.128 A, with the minimum wave length at 0.06 A.

The 400 kilovolt x-rays with 2 mm Cu plus 1 mm Al filter has a half value layer of 4.5 mm Cu hence its average energy is 175 kilovolts and its average wave length is 0.0685 A with the minimum wave length at 0.03 A.

We have neglected the portions of the beam whose wave length is greater than 1.2 A, since everything beyond this wave length has only a superficial effect. We have also neglected the absorption in air since this effect does not have any appreciable importance even in the case of the 100kv unfiltered beam. The average air distance in our experiments was approximately 30 cm.

The energy spectrum of the 100 kv, 200 kv and 400 kv beams is given in figure 3. Intensity in arbitrary units is plotted against wave length. The relative intensities of the different beams are not drawn to scale. A study of figure 3 shows that although it was possible to separate the 200 and 400 kv filtered beams only into two monoergic rays with a good deal of accuracy, this was not the case for the 100 kv unfiltered x-ray beam. The latter required separation into eleven different monoergic rays before the approximation was considered adequate for our purposes. The details of the separations

of the different beams as well as their intensities are listed in table IV.

Table IV

100 kv unfiltered x-ray beam separated into the following components

Wave length in Angstroms	Energy of ray in Kev	Relative Intensity
0.16	75.2	20
0.25	48.0	57
0.35	34.3	88
0.45	26.7	100
0.55	21.7	92
0.65	18.5	77
0.75	16.0	60
0.85	14.12	48
0.95	12.62	35
1.05	11.41	27
1.15	10.45	22
200 kv with 1 mm Cu filter:		
0.10	120	100
0.16	75	100
400kv with Cu andAl filters:		
0.045	267	100
0.16	120	100

From the definition of the roentgen we have the following relation:

r/sec = (1/k)mI .... Eqn 22

where

m = total absorption coefficient

I = energy flux = intensity of radiation in

ergs/ cm^2-sec.

k = constant = The product of the energy required to produce one ion pair in air and the number of ion pairs formed in air under ntp in 1 cm^3 by 1 r.

$= (32.5)(1.6 \times 10^{-12})(2.083 \times 10^{9}) = 0.1083$.

Therefore we may write:

$(I)/(r/sec) = k/m = 0.1083/m = ergs/cm^2\text{-}r$ Eqn 23.

In table V we have indicated the I/(r/sec) values for different energy photons in air and in average bone.

Table V

Energy in Kev	I/(r/sec) values for air	average bone
10	17.4	2.5
20	107.8	17.23
30	234	51
40	333	97
50	391	150
60	447	200
70	482	234
80	507	244
90	533	283
100	548	317
120	582	345
270	758	408

It should be noted that the values listed in table V probably will not conform with the values normally encountered in the literature. The reason for this is twofold. First, we have used the total absorption coef-

ficient, m, instead of subtracting the Compton scatter coefficient, m - $_{s}s$, as is done in the literature, and second, we have used the latest absorption coefficient values and have made a choice of the best available data after comparing the results of the different investigators. These two factors may lead to a considerable difference in the values of table V and current values found in the literature. A study of table V makes it clear that the energy flux necessary to produce one roentgen in air is considerably less for 10 kilovolt x-rays (only 17.4 ergs per cm^2 is required at this low energy) than for 100 kilovolt x-rays (which require 548 ergs per cm^2 for one roentgen). And in the case of bone this difference is even more striking (2.5 as compared with 317). With the data available it is possible to determine the contribution of the different components of the x-ray beam to the total dosage delivered. An example will illustrate the indicated method:

> The relative intensity of the 16 kilovolt component of the 100 kv unfiltered beam is 60 (see table IV). From an extrapolation of the data contained in table V we note that the number of ergs per cm^2 required to produce one roentgen of dosage in air is 64. Hence we can say that

the percentage contribution of the 16 kilovolt component to the total of the beam is (60/64)/7.56 where 7.56 is the summation of all such components in the 100 kv unfiltered beam. The results of all these calculations are listed in table VI.

table VI

100 kv unfiltered beam

Wave length in Angstroms	Percentage contribution of different components of the beam to the total dosage of the beam in: air	average bone	bone/air ratio
0.16	0.5	1.16	6.3
0.25	2.0	5.4	
0.35	4.0	16.3	
0.45	7	36.8	
0.55	10	57.8	
0.65	11	77	
0.75	12	79.3	
0.85	13	90.31	
0.95	13.5	92.51	
1.05	12.5	69.41	
1.15	14.5	104.1	
	100	630	

200 kv filtered beam

0.10	45	70.4	1.71
0.16	55	101.2	
	100	171.6	

400 kv filtered beam

0.045	41.5	78.2	1.708
0.10	58.5	92.6	
	100	170.8	

We have indicated in table VI the contribution of the different components of the beam not only in air but also in bone. The bone to air ratio of 6.3 for the un

filtered the beam as compared to the ratio of 1.71 for the unfiltered beam is a truer picture of the differential absorption of x-rays in bone and air than would be obtained by a simple comparison of the absorption coefficients involved. Most studies on this subject content themselves by merely quoting the absorption coefficients of air, water and bone and presume that such information is sufficient to the clinical radiologist.

E. Multiple Scatter as Contrasted Against Filtration Effect of Bone.

Selling and Osgood (35) make the statement that lymphatic tissue is more severely damaged by external radiation than bone marrow which is partially protected by it bony envelope. It is our purpose to test the validity of this statement first from theoretical considerations an then through animal experimentation. With the information contained in tables V and VI and depth dose data normally available in any medical journal devoted to radiology we have determined the depth dose relations of the three different x-ray beams used in our experiment. The results are tabulated in table VII below and represented graphically in Figure 4.

Assuming the x-ray beam first goes through 1 cm of soft tissue and then passes through 0.5 cm of hard bone before reaching the marrow, then the bone marrow receives 47.2% of the 100 kv unfiltered beam, 89.7% of

the 200 kv filtered beam and 97.6% of the 400 kv filtered beam. However, it should be noted that these results refer only to the primary beam and do not take into consideration multiple scatter. Thus considering only the primary beam and single scatter we note that the bony envelope of the marrow protects it considerably from relatively low energy radiation. Plesset and Cohen have shown recently (March 1951) that for distances small compared to the mean free path of photons the intensity of the beam or ray is accurately given by the transmitted unscattered radiation and the singly scattered photons (41). The mean free path is defined as the reciprocal of the absorption coefficient, 1/m . They also state that for distances of the order of a mean free path and greater the contributions from the photons scattered twice, three times etc. becomes increasingly great. We have listed below in Table VIII the the mean free path for different energy photons, but we have listed two separate mean free paths, one being the 1/m relation and the other, $1/(m - {}_{s}s)$. In this case it makes a great deal of difference whether we assume that m or $m - {}_{s}s$ represents the real absorption of energy in the human body. It is not our purpose to recommend whether m or $m - {}_{s}s$ should be used, or whether a value intermediate between the two should be used. However, we have consistently assumed the m should be used in our thesis, with the condition that the $m - {}_{s}s$ term values should always be included if such substitution leads to significantly different results.

Table VII

Thickness of soft tissue in Cm.	Percentage diminution of energy for: 100 kv beam unfiltered	200 kv beam filtered	400 kv beam filtered
0.5	94	98	100
1.0	85	94	99
2.0	69	92	94
4.0	45	71	79
8.0	19	43	51

Table VIII

Energy	1/m in Cm.		$1/(m - {}_s s)$ in Cm.	
in Mev	water	average bone	water	average bone
0.02	1.3	0.16		
0.03	3.0	0.32	5.6	0.54
0.10	6.7	2.92	41.1	11.5
0.30	9.6	4.9	36.4	18.2
0.50	11.6	6.0	33.3	18.0
1.0	16	8.4	36.4	19.1
5.0	38	19	57	28.6
10	50	26	68	31
15	58	30		
20	62.5	32	74	33.8
30	67.5	31	74	32.7
40	69	30	73.5	30.8
50	70	29	71.5	29.7
100	69	27	66.7	27.0
0.022	1.47	0.18 (100 kv Beam)	2.0	0.15
0.095	6.25	2.93 (200 kv Beam)	41.7	20.0
0.175	7.15	3.30 (400 kv Beam)	41.7	31.2

If we accept the work of Plesset and Coehn as referenced above, then we must assume that the multiple scatter is inversely proportional to the energy of the incident radiation and directly proportional to the thickness of the absorber. We note that if the multiple scatter is reduced

then the degradation of energy is reduced and this decreases the probability of photoelectric absorption by the calcium of the bone. If superficial x-rays or Grenz rays (10 kv or less) are used they cannot penetrate very much to do any appreciable damage to bone. If high energy x-rays are used (from 1 Mev to 25 Mev) then the multiple scatter is kept to a minimum and the bone is not damaged to any greater extent than the soft tissue elements. However, if x-rays of an intermediate energy are used such as 50 kv to 800 kv (especially if the beam is not filtered), then the bone receives maximal damage as compared to the soft tissue. This is because the intermediate energy x-rays are scattered a number of times after they penetrates into the body and this causes a great reduction in the energy of the primary beam, hence the probability of the photoelectric absorption in bone increases fifteen-fold over that of soft tissue since the bone contains a large percentage of calcium ($Z = 20$) as compared to soft tissue (where the highest Z is eight normally). It is the main purpose of this thesis to suggest to the clinical radiologist the type of x-ray beam to use in order to reduce the damage to the bone while doing maximal damage to the soft tissue tumor elements. The previously mentioned experiment of Wynen in 1929 (as reported by A Desjardins(3)) seems to confirm the contention of Plesset and Cohen concerning the extent of multiple scatter, because Wynen was able to show experimentally that seeds inclosed within bone received more damage when irradiated as

compared to seeds inclosed in muscle and receiving the same type and the same dose of radiation. This fact suggest that the filtration due to the bony envelope as suggested by Selling and Osgood (33) does not give the complete picture of radiation damage, but that the radiation damage produced by secondaries or by multiple scatter must be taken into consideration, and it is our contention that for low or intermediate x-ray energies the excessive biological damage produced by multiple scatter overcomes any beneficial effect of filtration as calculated from the primary beam and single scatter.

Since multiple scatter is proportional to the thickness of the absorber, we decided to use dogs as the experimental animal rather than guinea pigs, mice or rabbits. Also the hematological response to radiation exposure of the dog is quite similar to that of the human being, but this is not true for r abbits and other small animals normally employed in biological laboratories.

We believe that despite the work of Wynen, and despite the calculations of multiple scatter by Plesset and Cohen, a quantitative formulation of multiple scatter has not yet been developed. It is because of this that we decided to actually test the filtration vs multiple scatter effects experimentally in test animals.

IV EXPERIMENTATION

A. Animal Experimentation

A total of eleven dogs were used for the experiment. The dogs were irradiated with three different beams of x-rays. The details of the quality of radiation is given in the discussion of each individual dog. In every case the irradiation was local. When the front legs of the dogs were exposed, the center of the beam was made to impinge upon the center of the radius and the ulna. In each case the exposure was upon the lateral surface. When the hind legs were exposed the center of the beam was made to impinge upon the center of the tibia, and the exposure was upon the lateral surface. Total blood counts were made upon the dogs before and after exposure. It was found that this type of local irradiation did not effect the blood count at all if the rest of the body of the dog was well protected with 0.10 inches of lead. In the case of the first dog cited below there was a decrease in the total white blood cells, but it was found that this was due to inadequate shielding. When the body of the dog was completely and thoroughly covered with 0.10 inches of sheet lead there was no change in the total blood count even when the dose was increased to 2000 r. We have indicated below first the details of irradiation of each dog and the macroscopic effects of radiation upon the bone as

indicated during autopsy, and following this we have indicated some of the histological effects of radiation upon bone.

1. Details of the Method of Irradiation of the Different Dogs and a Study of the Macroscopic Effects of Local Irradiation Upon the Bones of the Dogs.

Dog # 9673

220 kv x-rays with 0.5 mm Cu filter, fsd 25.4 Cm., 492 r / 4 minutes given to the front right leg, 984 r / 8 minutes given to the hind right leg. Dog sacrificed 49 days after irradiation. Epilation of the right hind leg fourteen days after irradiation, recovery 28 days after irradiation. Upon autopsy the organs were normal in gross appearance. The right and left radius were cut at the center at right angles to the long axis of the bone for histological study. The cortex of the bone of the right leg as compared to the left leg did not indicate any thickening. The bone marrow appeared to be yellow to yellowish red and fatty with some evidence of capillaries or blood vessels present on the endosteal surface of the diaphysis. There was no difference in the gross appearance of the bone marrow in the irradiated right legs as compared to the non-irradiated left legs.

Dog # 9867

90 kv x-rays without filter, fsd 25.4 Cm., 462 r per four minutes to front right leg, 924 r / 14 minutes to right hind leg. Dog sacrificed 65 days after irradiation. Epilation of right hind leg 10 days after irradiation,

recovery complete 60 days after irradiation. The gross appearance of the organs during autopsy was normal except for the spleen which was slightly enlarged. The radius was cut in the center and the appearance of the marrow and the diaphyseal shaft (bone cortex) of the irradiated right radius was compared with the control left radius. This comparison brought out a striking difference. The diaphyseal shaft of the right radius showed a marked thickening which was clearly evidenced to the naked eye.The thickening took place at the expense of the bone marrow. This thickening was not evident in the control left radius. The marrow in the center of the right radius was white, hyaline or gelatinous in nature and dry as compared to the yellow to yellowish white, fatty and moist marrow present in the center of the unirradiated left radius. An interpretation of this may be that the low kilovoltage x-rays apparently produce a more profound effect upon the bone and the bone marrow as compared to the relatively higher kilovoltage and filtered x-rays. This may be due to multiple scatter being present to a greater extent in the low kilovoltage,unfiltered beam as compared to the relatively high kilovoltage, filtered beam. X-ray pictures of the cross sections of the diaphyseal shafts of most of the dogs have been taken and are indicated in figures 5.

Dog # 9856

400 kv x-rays with 2 mm Cu + 1 mm Al filter, fsd 38.5 cm. 500 r / 9 minutes to front right leg, 1000 r / 18 minutes to right hind leg. Dog sacrificed 30 days after irradiation. There was no sign of any epilation or even erythemal effects during the thirty days before autopsy. The organs appeared normal during autopsy. The cortex of the right radius was the same thickness as the cortex of the left radius. The same applied to the irradiated and control tibia of the hind legs. The bone marrow of the right legs corresponded to the bone marrow of the left legs as far as visual examination was concerned.

Dog # 144 B

400 kv x-rays with 2 mm Cu + 1 mm Al filter, fsd 38.5 cm.,1500 r / 25 minutes to front right leg. Epilation in front right leg 32 days after irradiation at which time the dog was sacrificed. Organs appeared normal during autopsy. There was no noticeable thickening of the right radius bone cortex over that of the left radius,but the marrow at the center of the right radius was dry as compared to that in the left radius. The marrow in the center of the left radius was yellow, fatty and moist and appeared normal.

The marrow in the right radius was not only dry but it also showed areas which seemed to be evacuolated.

Dog # 143 B

100 kv x-rays without filter, fsd 12.8 Cm., 1500 r / 24.5 minutes to front right leg. Dog sacrificed 35 days after irradiation. Epilation 12 days after irradiation, this was then followed by swelling in the front right leg. There was no recovery of the swelling or epilation ofthe front right leg 35 days after irradiation at which time the dog was sacrificed. Autopsy brought out considerable abnormality in the organs probably due to an accident to the dog a considerable period before our experiments began. The spleen of the dog was divided and the left kidney showed a constriction in the middle. There was no noticeable thickening of the right radius cortex over that of the left radius. The marrow in the right radius, however, was dry, evacuolated and shrunken. The marrow in the left radius was yellow, fatty and moist and appeared to be present in greater amount than in the right radius.

Dog # 142 B

100 kv x-rays without filter, fsd 12.8 Cm., 1900 r / 33 minutes to front right leg. Dog was sacrificed 32 days after irradiation. Complete alopecia and necrosis of the skin occurred 18 days after ir-

radiation. The skin condition deteriorated until the 22nd day at which time the dog was sacrificed. The organs appeared normal during autopsy except for a distention in the gall bladder. There was a significant thickening of the right radius as compared to the left radius cortex. Again this thickening seemed to be at the expense of the bone marrow rather than a thickening of the external diameter of the shaft. The diaphyseal marrow at the center of the right radius was yellow, dry and evacuolated, but that of the left radius was yellow, moist and fatty.

Dog # 536 B

This was a control dog. Autopsy showed normal organs. The bone marrow was yellowish tinting towards reddish yellow at the epiphyseal surface of the shaft. The marrow was fatty, moist and did not show any vacuoles.

Dog # 535 B

200 kv x-rays without filter, fsd 30.25 Cm., 1100 r / 4.5 minutes to right front leg. 100 kv x-rays without filter, fsd 28 Cm., 1135 r / 14 minutes to front left leg. Dog sacrificed 10 days after irradiation. No epilation up to time of autopsy. Autopsy normal. The right front leg which received the 200 kv x-rays had a yellowish red marrow which was moist but highly evacuolated. There appeared to be no visible thickening of the cortex of the bone at the center of the right radius. The left radius, which was irradiated with

100 kv x-rays there was some visible evidence of the thickening of the cortex at the center of the right radius, but there was some question whether this was due to the white gelatinous marrow or actually due to osteitis (calcification). Hence, x-ray pictures were made(see figures 5 and 5 a) which indicated that this was not true increase in the width of the cortex of the radius. It should be noted that only ten days had elapsed between irradiation and autopsy in the case of this dog. Hence it is assumed that true increase in the thickness of the shaft of the bone occurs after more than ten days from date of irradiation. Since dog # 9867 showed this effect 65 days after irradiation and dog 142 B showed this effect 32 days after irradiation (but with 4 times the dose administered to dog # 9867), we suggest that this 'productive osteitis' which tends to thicken the cortex of the bone at the expense of the bone marrow occurs a pproximately a month after irradiation for the order of magnitude of the dosage used here. The marrow of the left radius was yellowish white in appearance, dry and very much reduced in volume.

Dog # 564 B

100 kv x-rays without filter, fsd 29.6 Cm., 432 r / 6 minutes to front right leg. 220 kv with

1mm Cu + Thoreaus # filter, fsd 18 Cm., 445 r / 3.5 minutes to the front left leg. Dog sacrificed ten days after irradiation. No epilation. Autopsy normal. There was no thickening of the cortex of the left or right radius that could be observed visually. Marrow of left and right legs quite similar with the exception that the right leg marrow is somewhat more reddish in color, not as dry and not vacuolated to the same extent as the marrow of the left radius.

Dog # 957 B

100 kv x-rays without filter, fsd 22.5 Cm., 612 r/ 6 minutes to front left leg, 1100 r / 8 minutes to left hind leg. 200 kv x-rays, with Thoreaus # 2 filter, fsd 21.2 Cm., 600 r / 15 minutes to right front leg. Dog sacrificed 7 days after irradiation. Autopsy not performed. The four legs cut out and the radius, ulna and tibia studied. The radius and ulna of the left leg seemed to be similar in every respect to the radius and ulna of the right leg. This wastrue with respect to the thickness of the cortex and the nature of the marrow as far as visual examination could reveal. But there was a slight difference in the appearance of the marrow of the left and right hind legs (tibia). In the right tibia the marrow was moist, fatty and yellowish white in color. In the left tibia the marrow was yellowish red,

dry and there was some evidence of the beginning of osteitis. The thickness of the left and right tibia showed no visible difference.

Dog # 958 B

100 kv x-rays without filter, fsd 23.7 Cm., 1585 r / 14 minutes to right front leg; 200 kv x-rays with Thoreaus # 2 filter, fsd 24.5 Cm., 1540 r / 2[illegible] minutes to the left front leg. Dog sacrificed 7 days after irradiation. There seemed to be no difference in the appearance of the cortex of the bones nor in the marrow.

Dog # 939 B

200 kv x-rays with Thoreaus # 2 filter, fsd 23.2 Cm., 1300 r / 20 minutes to left front leg, 1300 r / 20 minutes to left hind leg. 100 kv x-rays without filter, fsd 24.5 Cm., 1300 r / 13 minutes given to the right front and the right hind legs. Dog sacrificed 7 days after irradiation. In this case there seemed to be a more significant change in the 100 kv x-rays as compared to the effect produced by the 200 kv filtered x-rays. The marrow of the left radius was considerably redder than the marrow of the right radius. The marrow of the left tibia was similarly redder than the marrow of the right tibia. There was no visible thickening of the left cortex as compared to the right one.

A review of the above-mentioned gross changes ob-

served during autopsy brings out the significant fact that there is an appreciable thickening of the cortex of the radius bone when it is irradiated with low voltage unfiltered x-rays which becomes increasingly evident with the passage of time from the initial date of irradiation. This same thickening was not observed for the higher voltage filtered rays used in the dosage range of our experiment. We believe that we have demonstrated perhaps for the first time in the literature that low voltage x-rays have a more profound biological effect than relatively high voltage, filtered rays.

2. Histological Studies

Since there were no facilities in this area to study histologically the undecalcified bones, we were forced to agree to have our bone samples decalcified and prepared for histological studies. The results were extremely disappointing in that the electrical method of decalcification worked only partially on the bone samples of our experiment. This necessitated the use of nitric acid to decalcify some of the bones, and in some cases one bone sample was put through both the electrical and chemical method of decalcification. Hence we were not able to obtain uniform decalcification. Worse than that, the relatively small cross sections of the radius of the bone, which we had hoped to get in one slide for study of endosteal and periosteal surfaces of the bone, were chipped

and severed and bore no relation to any recognizable surface of the bone. No samples of bone marrow could be prepared for adequate study. It was in view of these disappointing facts that we decided to repeat the experiment with the last three dogs mentioned above (Dogs # 937B, 938B, and 939B). However, due to the shortage of time the dogs were sacrificed seven days after irradiation solely for the purpose of studying the effect of the quality of radiation upon the bone marrow for we realize that calcification probably would manifest itself in a period of months rather than days. The results of the eight dogs of the earlier part of the experiments can be summarized simply as follows:

Some dead osteocytes in the lamellae, empty lacunae and some disappearance of canaliculi in the irradiated samples as compared to unirradiated bone. However, there was no histologically noticeable chnages between the low voltage unfiltered x-rays and the relatively high voltage filtered rays used in the irradiation of bone.

B. Backscatter and Port Size Studies

1. 200 kv with Thoreaus # 2 Filter

Using the Victoreen r-meter the following results were obtained:

a. For Large Port Size (10 Cm in diameter)

r-meter reading in air .... 100 %.

same but with wood backscatter ... 117.13 %

same but with wood & Al Backscatter.. 118.6 %

same but with wood & Pb Backscatter.. 108.5 %

b. For Small Port Size (4 Cm in diameter)

r-meter reading in air .... 100.0 %

same but with wood backscatter ...... 102.0 %

same but with wood & Al backscatter . 109.4 %

same but with wood and Pb " 103.0 %

2. 100 kv without filter

a. For Large Port Size

r-meter reading in air .... 100.0 %

same but with wood backscatter ...... 109.5 %

same but with wood & Al backscatter 108.0 %

b. For Small Port Size

r-meter reading in air .... 100.0 %

same but with wood backscatter ...... 102.5 %

same but with wood and Al " ...... 103.9 %

In all backscatter studies the beam was directed normal to the backscattering material. Sheets of Aluminum and lead were placed on wood and this is termed above as the backscatter from wood and Aluminum or from wood and Lead. The sheet metals were 0.5 Cm. in

width, and they were circular in shape with a diameter of 10 Cm. The wood was 5 Cm. in thickness.

It should be noted that the backscatter was considerably reduced as the port size was decreased and that this effect was more pronounced in the 200 kv filtered x-ray beam as compared to the 100 kv unfiltered beam. Since the backscattered beam must be considerably degraded in energy it would do considerable damage to bone, especially to superficial bone, such as the bones of the skull or hands. The bones imbedded well in soft tissue may escape injury from this type of backscatter due to the fact that the low energy backscattered rays probably cannot penetrate many centimeters of tissue.

V SUMMARY

1. A review of the literature indicates that although it had been recognized that bone absorbs more energy than soft tissue there was no clear cut evidence of the relative radiosensitivity of bone, no histological evidence of irradiation damage to bone (external irradiation), and certainly no evidence of the damaging effect of low voltage x-rays as compared to the less damaging effect of high energy, filtered x-rays.

2. We have reviewed the validity of the different absorption-scatter processes. This has led us to a criticism of the use of the concept of "effective atomic numbers" for compounds used as absorbers. We have recommended that from a knowledge of the chemical composition of a compound it is possible to determine the total absorption coefficient of the compound. Sample calculations are made and examples given in graph form. We have compared the absorption coefficients obtained by the various investigators and chosen the work of John A Victoreen for low energy photons and the comprehensive work of Snyder for high energy photon absorption.

3. We have made a detailed study of the energy spectrum of the different x-ray beams used in our experiment. It is our opinion that this leads to more accurate calculation of absorption than by merely using the average or mean energy of an x-ray beam obtained from a knowledge of the half value layer (HVL) of the beam, which at best would give an order of magnitude answer to the absorption prob-

lem even for a homogeneous 'phantom'. The HVL, or average energy of a beam is hopelessly inadequate for study of absorption in an inhomogeneous medium such as soft tissue and bone. The detailed energy spectrum of the different beams brings out the fact that the ratio of the energy absorption in bone as compared to soft tissue is 6.3 for the 100 kv unfiltered x-ray beam, 1.71 for the 200 kv filtered beam, and 1.708 for the 400 kv filtered beam.

4. The recent work of Plesset and Cohen shows that multiple scatter is proportional to the reciprocal of the linear absorption coefficient. Hence to reduce multiple scatter we should either use very thin absorbing media or energetic rays. The low voltage x-ray beam is degraded in energy by the extensive multiple scatter and this increases the probability of photoelectric capture by the calcium of the bone. The damage to bone caused by increased scatter cannot be calculated theoretically hence we have attempted to prove our point by animal experimentation. The filtration of x-rays by the bony envelope of the bone marrow is a maximum for the low voltage unfiltered beam. However, the increased biological damage produced by multiple scatter works against the beneficial filtration effect. Since

this cannot be studied quantitatively we have again resorted to animal experimentation to determine the question from the presence or absence of biological damage to the bone marrow.

6. The animal experimentation has brought out the significant fact that low voltage, unfiltered radiation increases the cortex of the bone at the expense of the bone marrow cavity. This was observed in two experimental animals, 65 and 32 days after irradiation. This effect was not observed in any of the animals irradiated with the relatively high voltage filtered x-rays. Damage to the bone marrow seemed to be proportional to the thickening of the bone cortex produced.

VI. RECOMMENDATIONS

It is recommended that in order to cause minimal damage to bone while irradiating soft tissue tumor elements, relatively high voltage x-rays be used with a maximum of filtration and with a small port size (to reduce backscatter to a minimum).

A. If the bone is imbedded deep in the soft tissues of the body, such as the pelvic bone, well collimated beams of the 22 Mev betatron would cause minimal damage to the bone as compared to soft tissue elements.

B. If the bone is near the surface of the body, such as the bones of the hand or the calvarium etc., 1 Mev, well filtered x-rays should be used with small port size. In the event that radioisotopes are used, any isotope which puts out monoergic gamma rays of approximately 0.5 Mev is recommended. Gold 198 is a good example of the type of radioisotope that may be used since it produces a monoergic gamma ray of 0.411 Mev energy. This gamma ray will go through superficial bone without multiple scatter, but its energy is still within the range where some beneficial shielding of the bone marrow may be obtained through the 'filtration' process. However, the 2.7 day half life may impose some practical restrictions to the external use of Gold 198.

C. If the bone is in an intermediate position (not superficial nor very deep in the body), then it is recommended that Cobalt 60 be used. The gamma rays of Cobalt 60 are 1.17 and 1.33 Mev. A well collimated x-ray beam which is highly filtered and which has an average energy of 1 Mev may also be

used provided the port size is small. Radium is not recommended because of the wide range of gamma energy photons in its equilibrium decay products (0.184 Mev to 2.198 Mev).

D. The above recommendations are based upon the fact that for bone near the surface of the body the mean free path of incident radiation more nearly approximates a value intermediate between $1/m$ and $1/(m - {}_{3}s)$, reference Table VIII. For this reason the 0.411 Mev gamma rays of Gold 198 (or 0.5 Mev gamma rays from any radioisotope) is considered the best source of irradiation external to the body. For bone deeply imbedded in tissue, it is presumed that the mean free path of the incident radiation is given by the $1/m$ value, hence the x-rays from the 22 Mev betatron were recommended, since at this high energy the mean free path is a maximum (in bone) as shown in Table VIII. For bone that is intermediate between the superficial and the deeply imbedded cases, the gamma rays from Cobalt 60 or its equivalent were recommended, because the mean free path for this type of radiation is sufficient to produce only single scatter, and there is no point in using more penetrating radiation. In all of the above-mentioned recommendations it has been assumed that the beam will be very small in cross section, well collimated, and that the tumor area would be attacked from different directions with a number of such beams.

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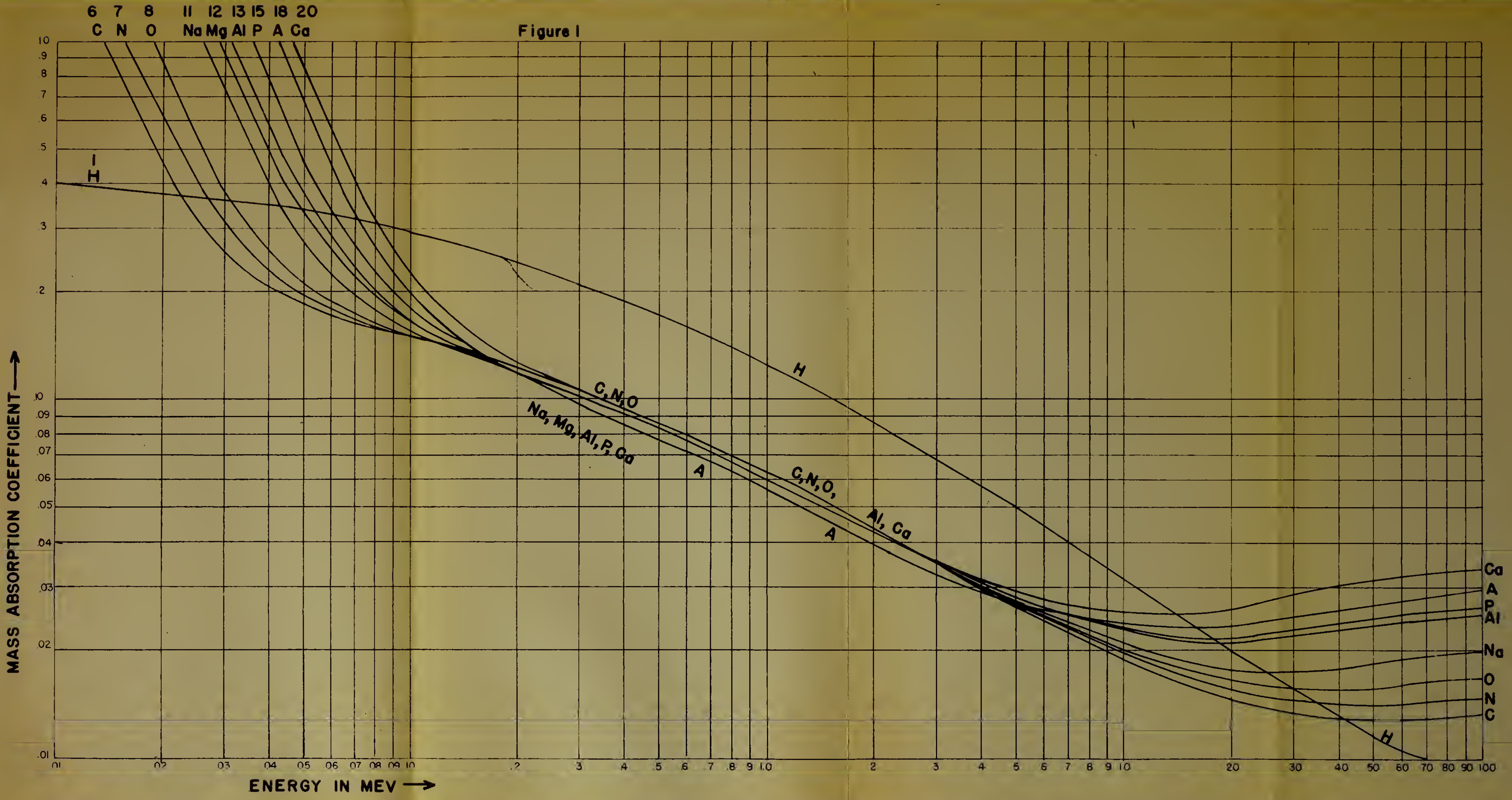
Figure I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1 H
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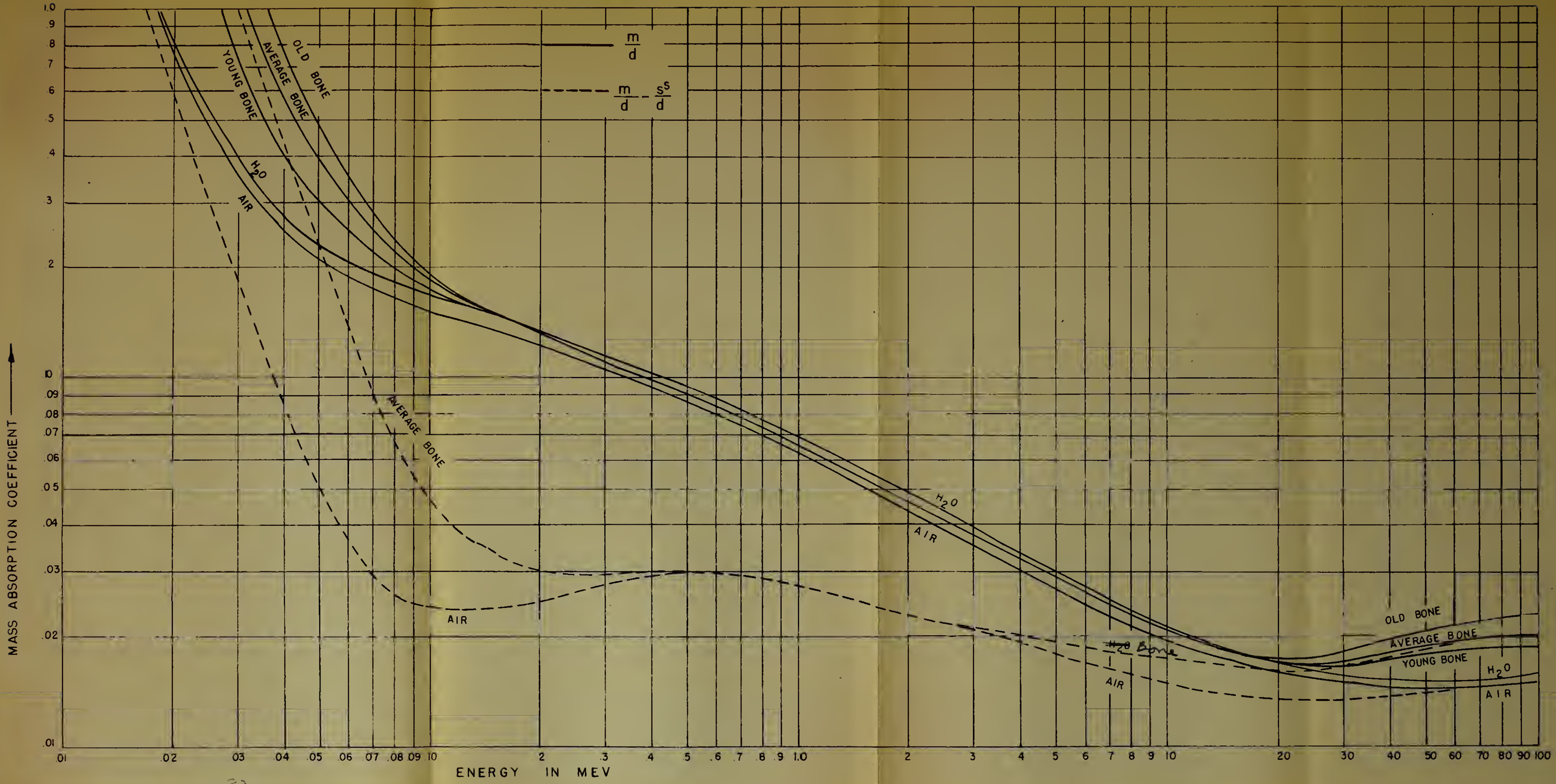
FIGURE 2



MASS ABSORPTION COEFFICIENT
ENERGY IN MEV
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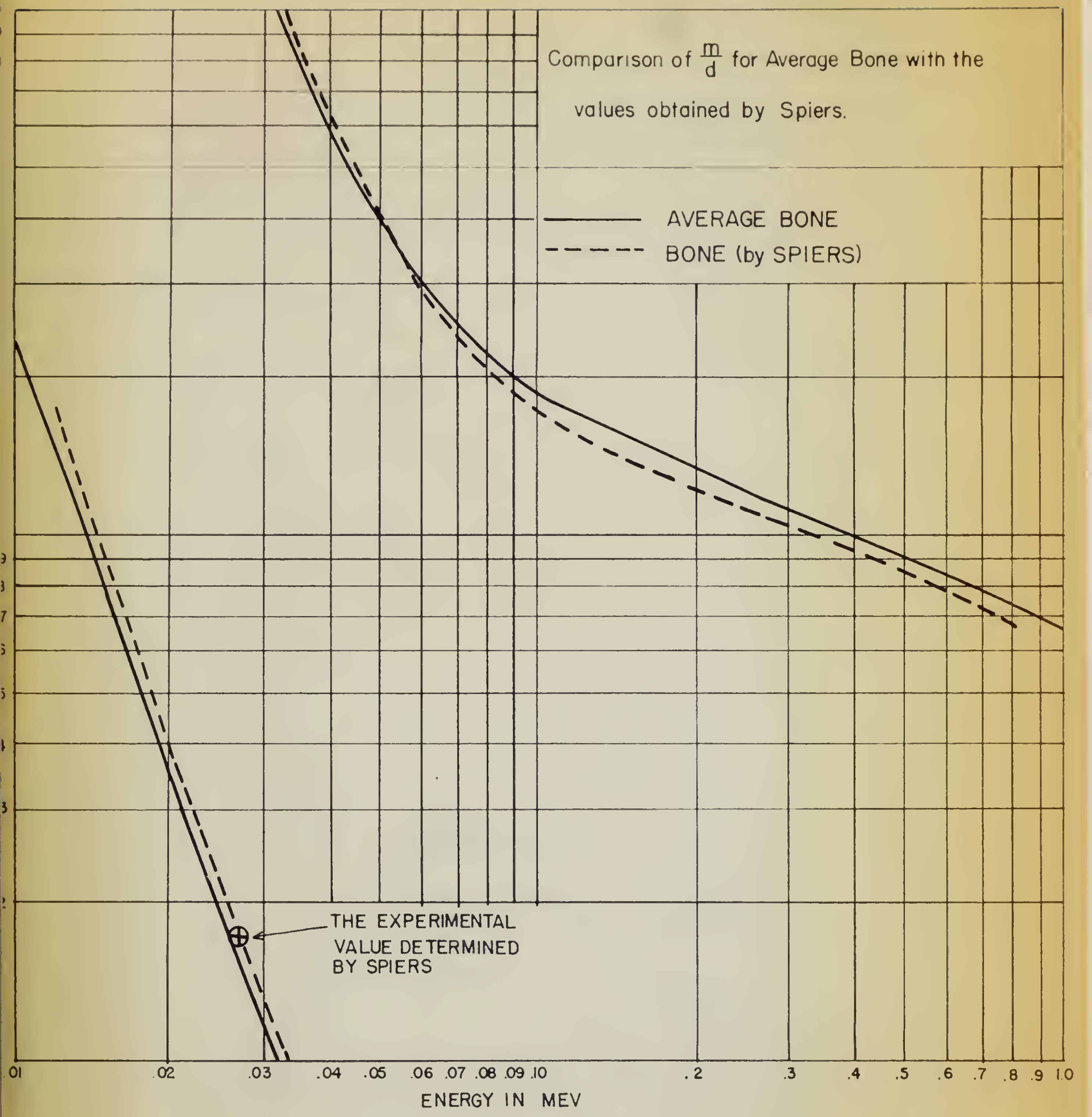
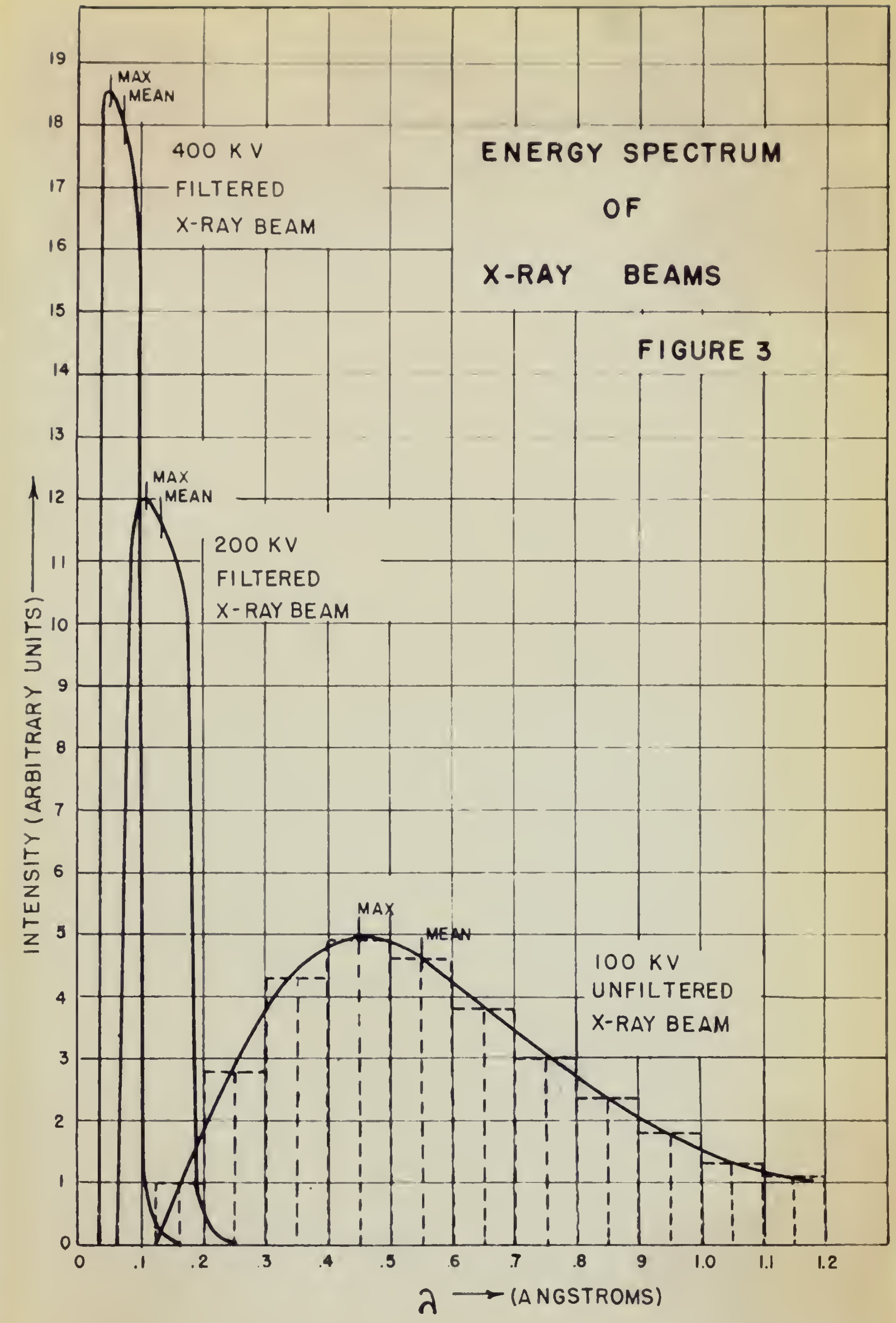
80
90
100
$\frac{m}{d}$
$\frac{m}{d} - \frac{s^s}{d}$
OLD BONE
AVERAGE BONE
YOUNG BONE
H_2O
AIR
AVERAGE BONE
AIR
H_2O
AIR
H_2O Bone
AIR
OLD BONE
AVERAGE BONE
YOUNG BONE
H_2O
AIR

32

FIGURE 2A

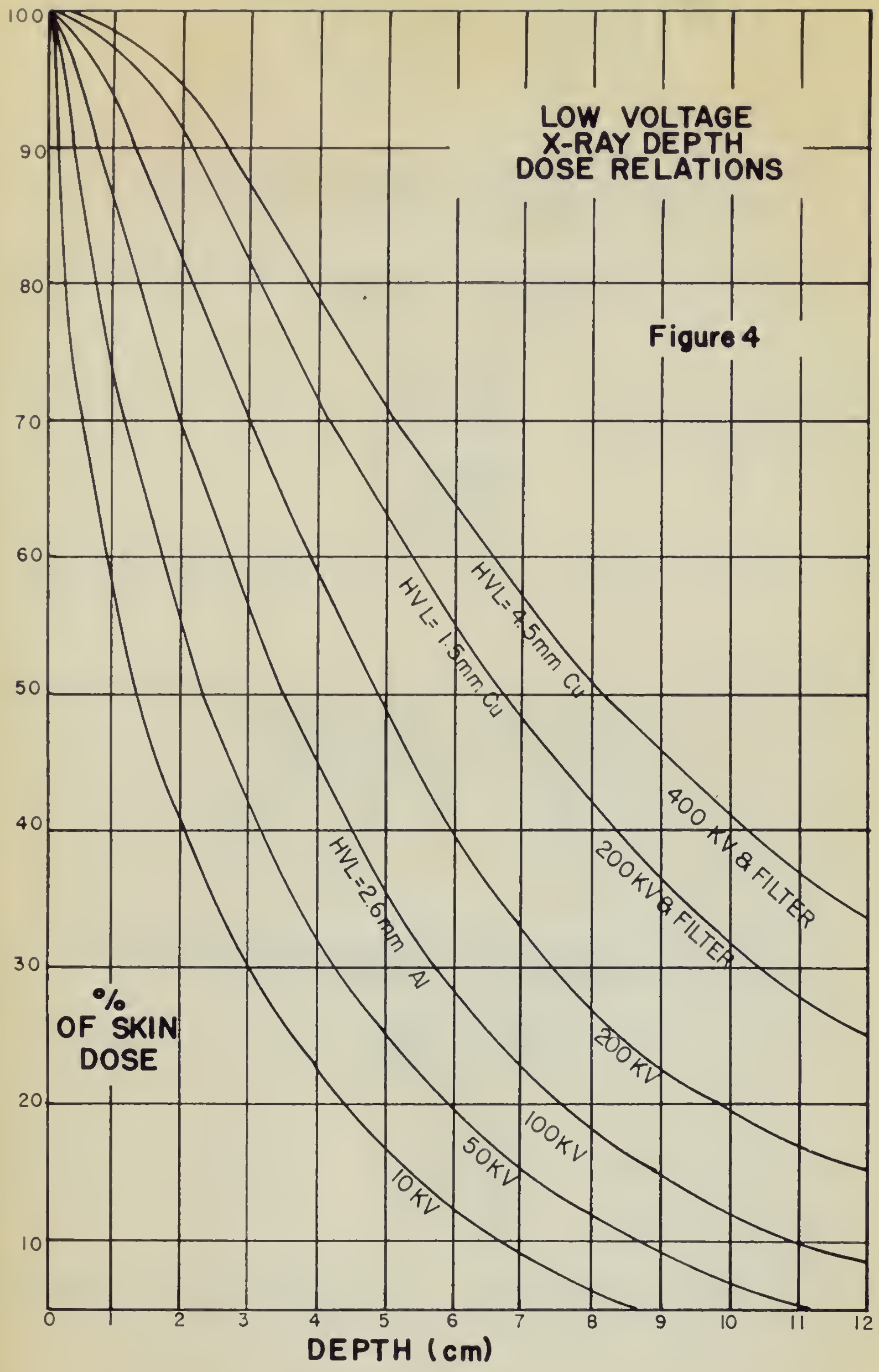


Comparison of $\frac{m}{d}$ for Average Bone with the values obtained by Spiers.



ENERGY SPECTRUM OF X-RAY BEAMS

FIGURE 3

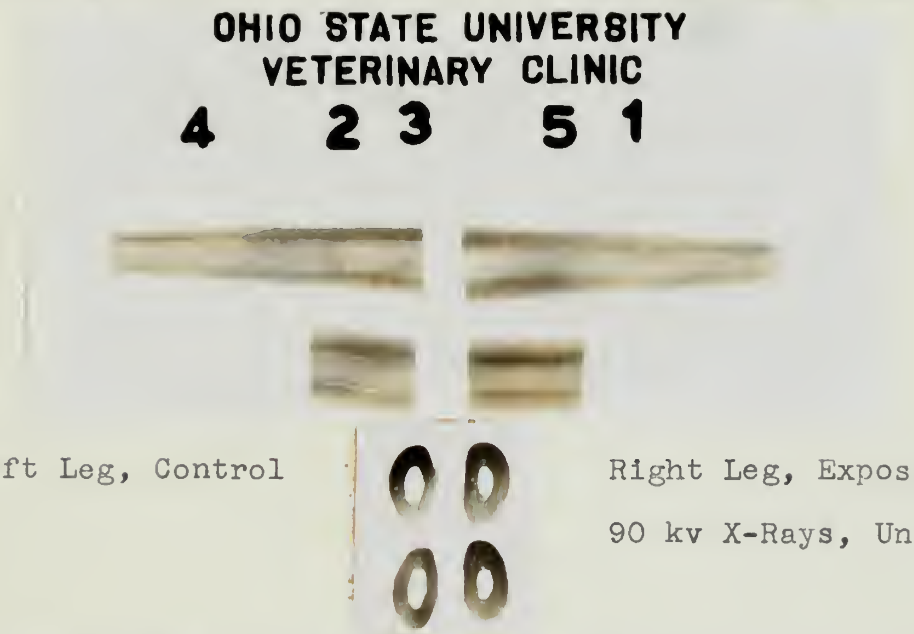


LOW VOLTAGE X-RAY DEPTH DOSE RELATIONS

Figure 4

FIGURE 5

X-Ray Photographs of Radius and Ulna of Dog # 9867



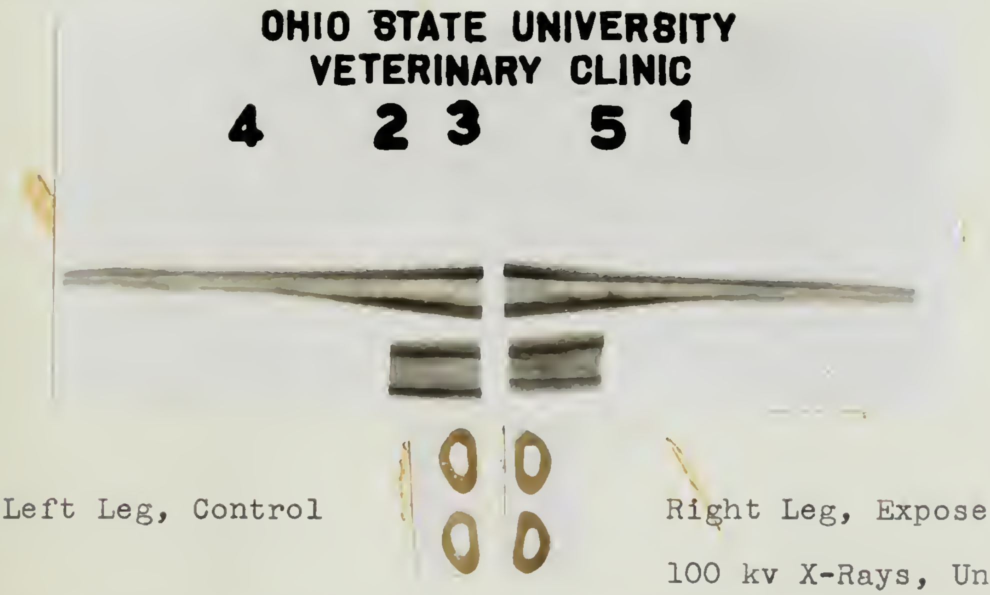
Left Leg, Control

Right Leg, Exposed to

90 kv X-Rays, Unfiltered.

Note thickened cortex of right radius in cross section as compared to the cortex of left radius

X-Ray Photographs of Radius and Ulna of Dog # 142 B



Left Leg, Control

Right Leg, Exposed to

100 kv X-Rays, Unfiltered.

There is a beginning of a thickened cortex of the right radius shown in cross section at the lower right hand side.

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